

Cerebral White Matter Injuries Following a Hypoxic/Ischemic Insult During the Perinatal Period: Pathophysiology, Prognostic Factors, and Future Strategy of Treatment Approach. A Minireview

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Abstract: Recent advances in medical care have significantly improved the survival rate of neonates who suffer a hypoxic/ischemic event, before, during, or after birth. These infants are extremely vulnerable to brain injury and are at high risk of developing motor and cognitive abnormalities later on in life. The regional distribution of perinatal brain injury varies, and depends primarily on; the severity, pattern and type of insult, the metabolic status, and on the gestational age. The principal neuropathological substrate that is affected in the premature infant is cerebral white matter. The aim of this article is to re-examine the current knowledge on the ischemic pathophysiology of all cellular components that comprise the white matter, predict the consequences of the long-term neurological outcome, and analyze possible therapeutic strategies. Although oligodendrocytes have long been regarded as the hallmark of perinatal white matter injury, axons, astrocytes and microglia, all contribute to the complex pattern of brain injury that occurs in this cohort of individuals. It is hoped that a better understanding of the pathophysiology of white matter injury and its underlying prognostic factors, may lead to the development of new therapeutic strategies for such a complex and debilitating condition.

Keywords: Perinatal ischaemia, periventricular leukomalacia, cellular mechanism, cerebral palsy, prognostic factors, treatment approach.

INTRODUCTION

Ischemic injury of preterm infants must be considered a major issue in today's society. The incidence of perinatal stroke has been estimated at one in 1600 to 5000 births worldwide [1-3], but its occurrence is probably underestimated due to the variability in clinical and diagnostic criteria. Infection/inflammation and ischemia/reperfusion injuries are the two main mechanisms in the pathogenesis of Periventricular Leukomalacia (PVL) [4]. There are a number of well established risk factors that predispose to perinatal brain injury. According to a recent classification, such factors can be divided into: maternal disorders (infertility, pre-eclampsia, chorioamnionitis, substance abuse), placental disorders (placental thrombosis, abruption, infection), blood disorders (polycythemia, disseminated intravascular coagulopathy, Protein S and C deficiency, antiphospholipid antibodies), homocysteine and lipid disorders, cardiac disorders (congenital heart disease, patent ductus arteriosus, pulmonary valve atresia, cardiac surgery), infectious disorders (meningitis, systemic infection), and other miscellaneous disorders (vascular maldevelopment, arterial dissection, trauma, dehydration, catheterisation) [5]. Major advances in medical treatment have led to the survival of almost 90% of low birth weight infants [6] but about 10% of them later develop spastic motor deficits [7-9], and about 20-25% later exhibit cognitive, attentional, behavioural, and/or socialisation defects that significantly impair their quality of life [10-12]. PVL is the most common cause of brain injury in premature infants [13] and results from a hypoxic/ischemic insult during the high-risk developmental period of 23 to 32 weeks of gestation [14], and to a lesser extent, as a result of germinal matrix intraventricular haemorrhage with asymmetric necrosis of the periventricular white matter [15]. The pathogenesis of PVL comprises systemic infection and inflammation, and

maturation-dependent intrinsic vulnerability of premyelinating oligodendrocytes [16]. However, white matter damage in PVL is not restricted to oligodendrocytes. Dammam *et al.* [17] suggested that white matter damage due to PVL involves deficits in oligodendroglia, loss of axonal fibres, microgliosis, and astriogliosis (Fig. 1).

OLIGODENDROCYTE INJURY

Oligodendrocyte injury has long been regarded as the hallmark of PVL. Oligodendrocyte development occurs in four stages: early oligodendrocyte progenitor cell (OPC), late OPC (also called premyelinating oligodendrocytes), immature myelinating oligodendrocyte, and mature myelinating oligodendrocyte [18]. Back *et al.* [19] reported that late OPC are significantly more vulnerable to ischemia than early OPC. This maturation-sensitivity of the late OPC leads to preferential white matter injury in the neonate [16] and coincides with the high-risk period for PVL in humans [20]. Injury of the late OPC is therefore regarded as the main pathological lesion seen in cerebral white matter in the neonate [21]. The major factors that underlie the maturation-dependent susceptibility of the late OPCs are: (i) abundant production of reactive oxygen and nitrogen species in combination with delayed development of glutathione antioxidant defences, (ii) acquisition of Fe²⁺, and (iii) exuberant expression of the major glutamate receptors (GluRs) (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors deficient in the GluR2 subunit and of N-methyl-D-aspartate (NMDA) receptors (both Ca²⁺-permeable)) [16].

Although the vulnerability of the late OPC is one of the hallmarks of the increased susceptibility of white matter injury to ischemia during development, as we previously reported, the immature myelinating oligodendrocytes also contribute to the continuum of white matter vulnerability following ischemia [22, 23]. Thirty minutes of oxygen-glucose deprivation (OGD) is sufficient to kill almost 70% of oligodendrocytes, and the percentage of dead oligodendrocytes in neonatal mice (P10 - post-natal day 10) is significantly higher than that in older age groups (Fig. 2). Since in the mouse optic nerve immature myelinating oligodendrocytes

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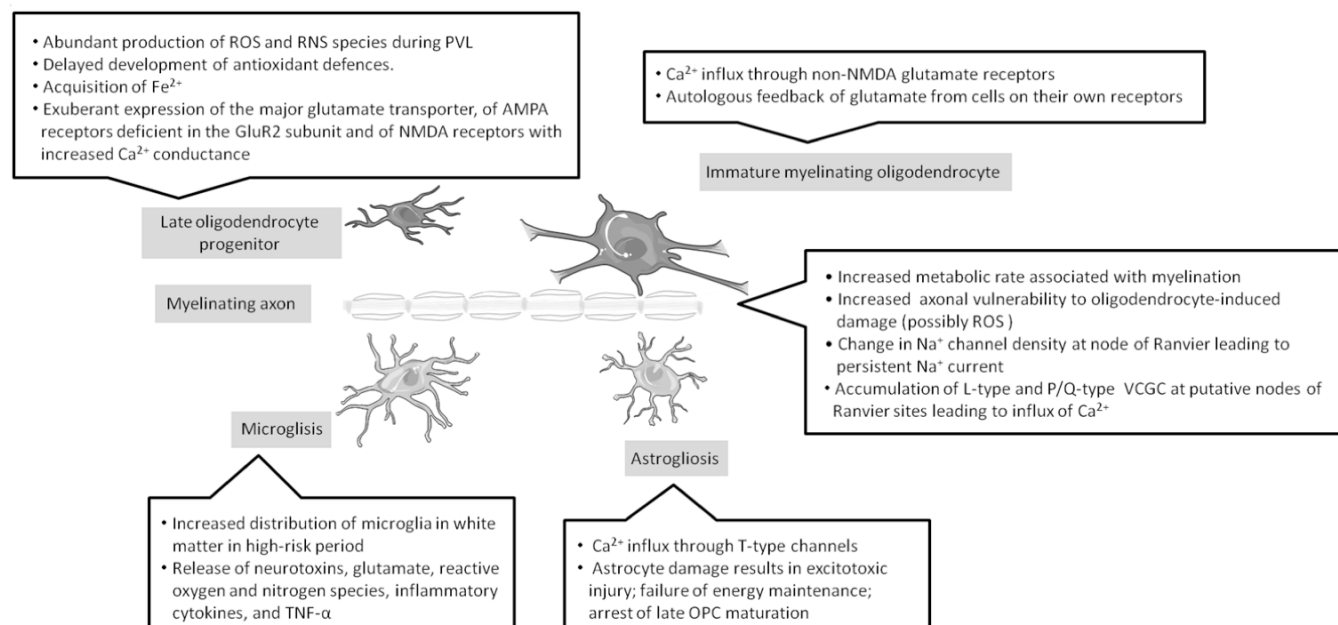


Fig. (1). Cellular mechanisms of injury in perinatal white matter ischemia.

Cartoon depicts the stage-specific mechanisms that are thought to contribute to the heightened sensitivity of all components of white matter injury during the perinatal period.

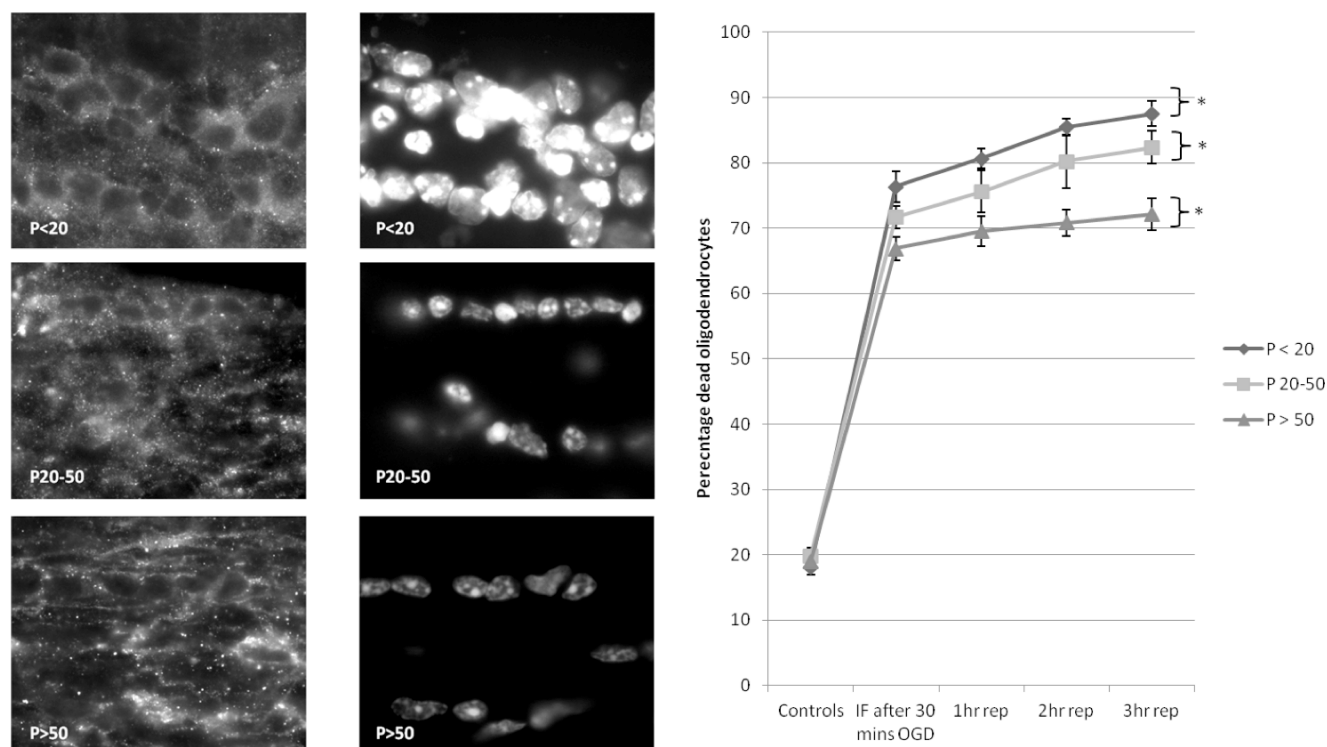


Fig. (2). Heightened vulnerability of immature myelinating oligodendrocytes to ischaemia.

Left: Cropped sections from high power micrographs (X60) of optic nerve sections from 3 different age groups (P<20, P20-50, and P>50) immunostained with anti-APC (left) and Hoechst stain (right) after 60 mins OGD. Optic nerves from P<20 mice had a greater number of pyknotic nuclei when compared to older age groups. Right: Comparison of the percentage of dead oligodendrocytes following ischemia between different age groups. There was a statistically significant difference (* $p \leq 0.05$) in the percentage of dead oligodendrocytes between the different age groups after 30 mins of OGD. APC +ve oligodendrocytes at P<20 were the most vulnerable to injury. (OGD – Oxygen-glucose deprivation; IF – immediately fixed; 1hr – 1 hour reperfusion; 2hr – 2 hours reperfusion; 3hr – 3 hours reperfusion).

predominate at around P7 to P10 [20], our results suggest that immature myelinating oligodendrocytes are more vulnerable than mature myelinating oligodendrocytes. In cell cultures, mature oligodendrocytes (A2B5⁺/GC⁺) are more resistant to ischemia than immature ones (O4⁺/GC⁻) [24]. Results from these studies suggest that rapid ischemic cell death of immature oligodendrocytes is mediated by Ca²⁺ influx via non-NMDA glutamate receptors, and exacerbated by significant autologous feedback of glutamate from cells on their own receptors [24].

LOSS OF AXONAL FIBRES

The sensitivity of rat grey matter to anoxia and aglycaemia increases progressively from birth to adulthood; consistent with the rise in metabolic demand of this tissue [25, 26]. However, white matter does not follow a similar pattern. After a period of increased tolerance to ischemia (P3 mice), Fern *et al.* [27] reported an increased vulnerability to ischemia of white matter in terms of functional loss of conduction in P20-P50 mice. This vulnerability starts to decrease at P50, which is in agreement with our published observations [22], wherein the degree of ischemia-induced structural axonal injury in P20 - P50 mice is significantly higher than in any other age group (Fig. 3).

In the mouse optic nerve, myelination starts at around P7, with few axons having only one whorl of myelin at this age [28]. The rate of myelin deposition thereafter peaks at P21-P28, and from this point onward, the process of myelination is at its highest [29]. The period of low tolerance to ischemia observed [22] in mice between P20 and P50 coincides with this process of myelination, and the increase in sensitivity to ischemia can be attributed to the onset of the associated heightened metabolic activity [30-32]. Fowler *et al.* [33] proposed that myelination might increase axonal vulnerability to oligodendrocyte-induced damage, since perturbation of the oligodendrocyte-myelin-axon interaction in myelinated white matter

decreased axonal damage after AMPA administration in rats. Myelination is not the only contributor to this increased vulnerability, as Na⁺-channel density in optic nerve axons also varies with age. This starts from < 2/ μm^2 in the neonate [34], increasing up to the age of about P25, and declining during adulthood [35]. During myelination Na⁺ channels aggregate at the nodes of Ranvier, and ischemia causes an increase in density and a persistent non-inactivating Na⁺ current that leads to increased axonal calcium flux through reversal of the Na⁺/Ca²⁺ exchanger [36].

As we previously reported [23], large (> 0.4 μm in diameter) pre-myelinating axons are more sensitive to OGD than smaller pre-myelinated and myelinating axons. Blockade of NMDA and non-NMDA GluRs alone provides only partial protection from ischemic injury whereas addition of L-type and P/Q-type voltage-gated calcium channel (VGCC) blockers to these GluRs antagonists results in complete recovery of the compound action potential [23, 37]. Comparison of OGD-induced damage to small (< 0.4 μm) and to large (>0.4 μm) premyelinating axons shows that the former are protected by GluR blockers alone, whilst the latter needs addition of VGCC-blockers to confer protection [23]. This study shed light on the importance of VGCC in this age group, and on the pathophysiological mechanism of injury during ischemia in these very sensitive axons.

MICROGLIOSIS

Numerous studies have demonstrated that activated microglia trigger injury to immature white matter causing injury to surrounding neurons and glia through the release of neurotoxins, glutamate, reactive oxygen species, nitric oxide and inflammatory cytokines [38-40]. Other substances released from microglia, such as tumour necrosis factor- α (TNF- α), can increase the susceptibility of surrounding neurons and oligodendrocytes to ischemic injury [41]. It was also demonstrated that lipopolysaccharide-activated microglia

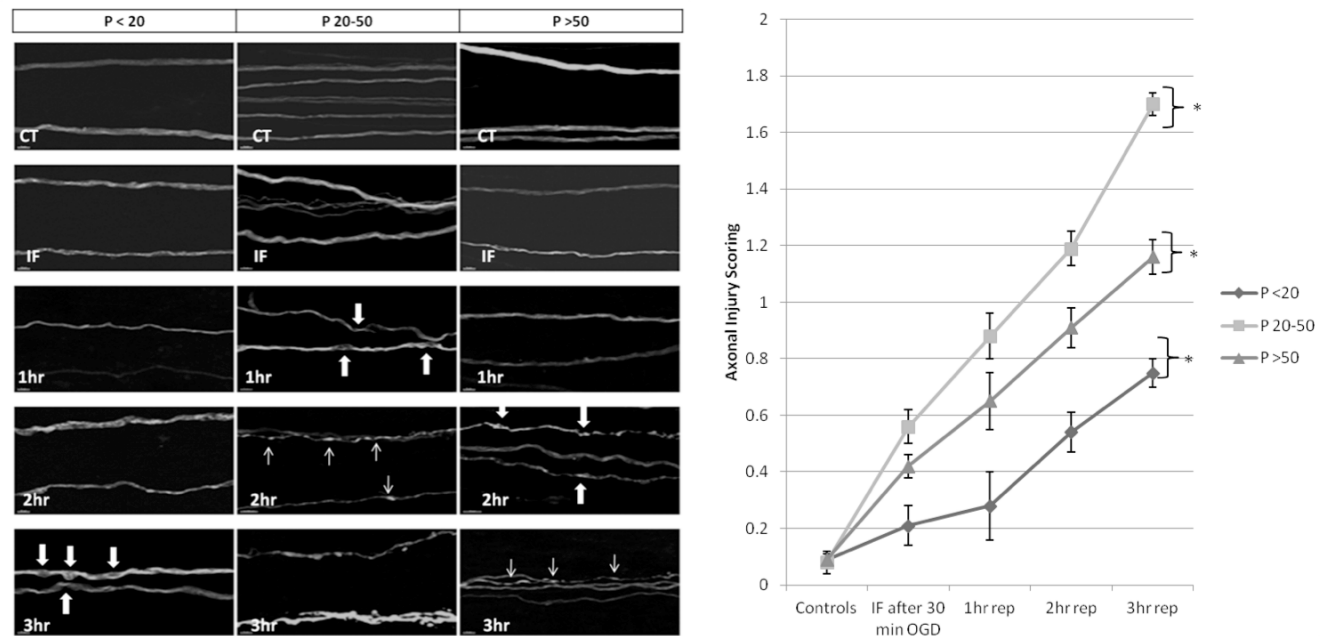


Fig. (3). Heightened vulnerability of actively myelinating axons to ischaemia.

Left: Confocal images (Magnification X 60 lens – X 400 digital zoom) of Thy-1/GFP-M mice from 3 different age groups following 30 mins OGD. There is progression of injury in all age groups, but features of axonal damage were first evident in P20-50 mice, followed by P > 50 mice, and finally P < 20 mice. Thick arrows mark axonal swelling; thin arrows mark beading and fragmentation. Right: Comparison of axonal injury following ischemia between different age groups. There was a statistically significant difference (* $p \leq 0.001$) in axonal injury score between the different age groups at each time point following 30 mins of OGD. P20-50 mice (box) were the most vulnerable to injury, and P < 20 mice (diamond) were the most resistant. (OGD – Oxygen-glucose deprivation; IF – immediately fixed; 1hr – 1 hour reperfusion; 2hr – 2 hours reperfusion; 3hr – 3 hours reperfusion).

adversely affected the survival and development of oligodendrocyte progenitor cells, reducing the production of myelin basic protein [42]. Therefore, disturbance of myelination in PVL is believed to be due to arrested maturation of premyelinating oligodendrocytes induced by nitrosative and oxidative mechanisms mediated by microglial cells [43, 44].

The density of microglia in the brain varies throughout development [45]. During the period of high sensitivity of the human brain to ischemia, activated microglia are concentrated in the cerebral white matter. This maturation-dependent distribution of microglia might also play a role in the selective white matter injury during this stage, since microgliosis is a prominent feature of cerebral white matter injury seen in premature infants [45].

ASTRIOGLIOSIS

Astrocytes play a vital role in the normal physiology of the human brain. They regulate synaptogenesis, neurotransmission, metabolic support, blood-brain barrier formation/maintenance, and actively participate in the innate immune response [46-48]. Therefore, they are likely to be involved in the cascade of pathological events that occur in the immature brain in response to infection and/or inflammation [46]. Neonatal white matter astrocytes are highly susceptible to ischemic injury [49, 50]. This high sensitivity is due to an exaggerated Ca^{2+} influx through T-type VGCC [51]. Damage to astrocytes causes impairment of astrocyte glutamate receptors resulting in the excessive accumulation of extracellular glutamate that contributes to the excitotoxic injury of oligodendrocytes and axons [52]. It also disrupts the homeostatic and metabolic regulation of glucose and lactate, with subsequent failure of energy maintenance [53]. Moreover, inhibitory factors released from reactive astrocytes arrest the maturation of late OPCs [54].

PREDICTORS OF LONG-TERM NEURODEVELOPMENTAL OUTCOME FOLLOWING NEONATAL ISCHEMIA

In the developing immature brain, ischemic brain injury predisposes to cerebral palsy, a non-progressive motor disorder of movement and posture, which is often accompanied by disturbances in sensation, perception, cognition, communication and behaviour [55]. Improved neonatal care within the last decade has led to the increased survival of preterm and low-birth-weight infants. However, this resulted in an increased risk of adverse long-term outcomes, especially with respect to cognitive and behavioural deficits [56].

The age and location of the insult are important determinants and predictors of neurodevelopmental outcome. There is considerable evidence that an early brain insult is associated with a broad spectrum of neuropsychological dysfunction [57, 58]. In fact, the onset of stroke at a younger age predisposes to an overall worse prognosis [59-61], weaker cognitive performance, and is subject to lesion location [62]. Westmacott *et al.* [62] reported that individuals who suffered a subcortical stroke (affecting the thalamus and/or basal ganglia axis) before the age of 28 days performed significantly poorer in terms of intellectual performance than older children with the same insult. In contrast, in the case of cortical strokes, the period of greatest vulnerability appears to be within 1 month and 5 years. In a more recent study, Studer *et al.* [63] found that cognitive outcome in children who suffered an acute ischemic stroke (defined as focal neurological deficit of acute onset confirmed by cranial Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) showing an infarction in a corresponding location) between 1 month and 3 years was worse than in older children. However they did not find any influence of lesion location (cortical or subcortical) to the overall outcome. They hypothesized that rather than lesion location, lesion size is a more valid predictor of overall outcome, since larger lesions disrupt a wider network of neural connections, resulting in worse cognitive outcomes. Maitre *et al.* [64] reported a similar finding; infants who suffered unilateral

periventricular hemorrhagic infarction had better motor and cognitive outcomes than infants with bilateral periventricular hemorrhagic infarction.

Preterm born very-low-birth-weight (VLBW: birth weight <1500g) infants are at an increased risk to develop perinatal brain injuries that will ultimately result in abnormal brain development [4, 9]. Several studies have investigated the relationship between perinatal brain injuries in VLBW survivors and brain development [65-67]. In a recent meta-analysis, de Kieviet *et al.* [68] summarised that VLBW infants who suffer perinatal brain injury develop smaller total brain volume with reduced volume of grey and white matter. Such injuries may influence cognitive development and performance [21, 68]. Aarnoudse-Moens *et al.* [69] reported a reduction in academic achievements and problems with behaviour, attention and executive functions in VLBW children that are correlated to the degree of immaturity at birth. A recent study by Bjuland *et al.* [70] investigated the difference in brain volumes and cognitive abilities between VLBW subjects and term born controls. They reported a reduction in absolute volumes of several brain structures (mainly thalamus, caudate nucleus, cerebellar white matter and corpus callosum) with the most immature and smallest VLBW birth infants having the most pronounced volume reduction. This decrease in brain volume was also correlated with a reduction in IQ levels, which suggested that perinatal brain injury associated with VLBW induces permanent deficits in cognitive abilities later on in life. Taylor *et al.* [71] also reported a significant correlation between IQ levels and cerebral white matter volume in VLBW adolescents.

Jakobson *et al.* [72] suggested that deficits in mental capabilities related to premature births are not due to prematurity per se, but from complications associated with it. This was further validated by Pavlova *et al.* [73], who reported no difference in mental calculation scores between term-born and premature-born babies with normal MRI findings. However, pre-term infants are prone to various complications, including late-onset sepsis [74]. This leads to white matter abnormalities later on life [75-77], since the preterm brain, in particular white matter, is highly vulnerable to damage by inflammation and ischemia [78]. van der Ree *et al.* [79] investigated the effect of late-onset sepsis in preterm children. The majority of preterm infants who survived the late onset sepsis showed a lower intelligence, impaired attention and verbal memory, and an abnormal motor outcome at school age (6 to 9 years). Moreover, multiple episodes of sepsis result in a worse outcome, possibly due to progressive white matter injury following recurrent infections [80].

Biomarkers have become increasingly utilised as non-invasive tools in the early diagnosis of various clinical conditions. Recently, Andrikopoulou *et al.* [81] reviewed some markers that can be used as early detectors of perinatal ischemia; indicators that may help in predicting the prognosis of such infants. Detection of nucleated red blood cells at birth reflects a response of the infant to perinatal hypoxia [82] and can be used for the assessment of the severity and early outcome after perinatal asphyxia [83]. Glial fibrillary acidic protein (GFAP) is a brain-specific cytoskeletal intermediate filament protein found in astrocytes. Studies have explored the use of this marker for the early diagnosis of patients with stroke [84]. Ennen *et al.* [85] observed significantly elevated GFAP concentrations in blood samples in patients with hypoxic-ischemic encephalopathy when compared with controls. Systemic infection is one of the main contributing factors to cerebral white matter injury [86], and therefore inflammatory cytokines may be useful as markers of the inflammatory response post-injury. Ellison *et al.* [87] found that pre-term infants with MRI-defined cerebral white matter lesions had higher levels of interleukin (IL)-6, IL-10, and TNF- α in their cerebrospinal fluid, than infants without such findings. Ramaswamy *et al.* [88] reported that serum and cerebrospinal fluid concentrations of IL-1b and IL-6 were predictors of abnormal outcome in

patients with hypoxic-ischemic injury. S-100 is a calcium binding protein and is a major component of the cytosol in glial cells. Qian *et al.* [89] reported elevated levels of this protein in neonates with hypoxic-ischemic encephalopathy. Gazzolo *et al.* [90] demonstrated that a high concentration of S100 had a sensitivity of 91.3% and a specificity of 94.6% for predicting the development of hypoxic-ischemic encephalopathy.

NEUROIMAGING ASSESSMENT OF PVL

Neuroimaging is a widely used tool to assess the severity of brain injury following foetal or neonatal ischemia, since the long-term outcome in such infants depends on the nature of the initial insult [91]. Cranial ultrasonography (US) is very useful for the detection of intraventricular hemorrhage and cystic PVL. It is readily applied at the bedside, does not involve ionizing radiation, is cost-effective, and can be used sequentially [92]. Multiple single, and multi-centre studies reported an association between cranial US findings and adverse neurodevelopmental outcomes [93-95]. The strongest predictors of subsequent cerebral palsy visualised on US are ventriculomegaly and white matter echolucencies [96]. Application of advanced techniques, including the use of high-resolution linear transducers and Doppler assessment of intracranial vasculature, assist in maximizing the value of this important tool [97]. However, cranial US has its limitations. Brain views are limited to what can be seen through the fontanelles [94] and only 30 % of white matter injuries are consistently detected with US. These include areas of necrosis, diffuse gliosis, cystic PVL, and ventriculomegaly due to periventricular white matter loss [98]. Inder *et al.* [99] reported that 55% of infants with a normal cranial US showed extensive signal intensity abnormalities or cystic changes in the cerebral white matter on Magnetic Resonance Imaging (MRI).

Multiple studies [100, 101] reported that MRI findings have a higher sensitivity and specificity to predict cerebral palsy when compared to cranial US. Woodward *et al.* [102] found significant associations between the qualitative measures of cerebral white- and gray-matter abnormalities on MRI, and the subsequent risks of adverse neurodevelopmental outcomes at two years of age. In addition, moderate to severe white matter abnormalities were predictive of severe psychomotor delay and cerebral palsy. In a recent study, Imamura *et al.* [103] investigated the relationship between MRI findings and neurodevelopmental outcome of children with PVL. They graded PVL based on MRI findings [104] as Grade 1, 2 and 3. Children with Grade 1 PVL had abnormally high signal intensity in the periventricular white matter on T2 and fluid-attenuated inversion recovery images, most commonly observed bilaterally in the trigone regions of the lateral ventricles. In Grade 2 PVL there was loss of the periventricular white matter in the regions with abnormally high signal intensities, and ventricular enlargement adjacent to the regions of the lateral ventricles. In Grade 3 PVL there was focal and extensive cystic changes in the white matter. Children with Grade 2 and 3 had severe neurodevelopmental delays with a high degree of motor impairment and cognitive disability. On the other hand, 56 % of infants with Grade 1 PVL had normal psychomotor development [103].

Radiologists routinely read clinical MRIs qualitatively. Although this is a useful technique for clinical decision-making, it does not provide quantitative values that can be used to monitor neurodevelopmental progress. Recent advances in MR imaging modalities provide new tools for researchers to assess quantitatively injury to brain structures. MR Diffusion tensor imaging is widely accepted for use in paediatric studies [105]. Using this technique on PVL patients, Wang *et al.* [106] reported a significant reduction in mean fractional anisotropy (FA) value (sensitive to axon size, density, organisation and degree of myelination) in a number of white matter tracts (corticospinal tract, internal capsule, arcuate fasciculus, posterior thalamic radiation, corona radiata, superior longitudinal fasciculus, and splenium of corpus callosum). These subjects

also showed various degree of cognitive and motor impairment. Cognitive functions are supported by a network of multiple interconnected cortical and subcortical regions, and the integrity of the connecting white matter is an essential tool for efficient cognitive processing [107]. Since there is a correlation between the FA value and cognitive function in terms of IQ score [108], Wang *et al.* [106] demonstrated that the disturbance of the cognitive ability in preterm children with PVL was significantly correlated to the disruption of white matter microstructure in widespread areas of the brain.

CURRENT AND FUTURE THERAPEUTIC APPROACH

To date, there is no known effective treatment for PVL. Apart from therapeutic hypothermia [109, 110], none of the proposed experimentally neuroprotective treatments have managed to find their places in standard clinical practice [111]. However, continuous research is being done to develop new therapeutic regimens to treat or prevent the development of PVL.

Glutamate excitotoxicity is a main factor in the pathophysiology of hypoxia-ischemia in the neonate. Magnesium is an NMDA receptor antagonist, and prevents neuronal influx of Ca^{2+} . The use of magnesium in clinical trials has produced conflicting results. One trial showed some neuroprotective benefit in term infants with severe asphyxia [112]. In another, Rouse *et al.* [113] reported a non-significant reduction in stillbirth or death in one year, but a statistical significant reduction in moderate to severe cerebral palsy. Anticonvulsant drugs, like memantine and topiramate also reduce glutamate toxicity by blocking NMDA and AMPA receptors respectively. These drugs were found to be highly effective in reducing brain injury following hypoxia/ischemia [114, 115]. Erythropoietin inhibits apoptosis, neuronal excitotoxicity, and inflammation. Infants with neonatal encephalopathy treated with this drug displayed a significant reduction in terms of mortality and disability [116].

Since reactive oxygen species are one of the hallmarks of perinatal ischemic injury, free radical scavengers have also been tested as possible therapeutic strategies. Antenatal administration of allopurinol was found to reduce the degree of hypoxic-ischemic encephalopathy in neonates exposed to foetal hypoxia [117]. Other anti-oxidants such as 2-iminobiotic and indomethacin were also found to be effective [118]. Antioxidant enzymes administered prophylactically during pregnancy reduced neuronal injury in rat pups subjected to hypoxia-ischemia [119]. Vitamin K has been shown to prevent oxidative injury to undifferentiated oligodendrocytes [120], but to date no clinical trials have been done to evaluate its potential to decrease inflammatory or ischemic injury during perinatal ischemia.

The role of pro-inflammatory cytokines in the pathophysiological cascade leading to neonatal brain damage is increasingly recognized. Postnatal systemic administration of Interleukin-1 receptor antagonist was found to preserve motor function and exploratory behaviour in rats following exposure to inflammation and/or postnatal hypoxia-ischemia [121].

In recent years, stem cell treatment has generated interest in many medical fields, particularly in conditions with irreversible organ damage and non-available specific treatment. Animal studies support the idea that cord blood and mesenchymal stem cells have a therapeutic effect in neonatal hypoxic-ischemic encephalopathy [122]. These effects have been attributed to immunomodulation, activation of endogenous stem cells, release of growth factors, and anti-apoptosis mechanisms [123]. Intranasal administration of mesenchyme stem cells in neonatal mice, reduced the brain lesion volume induced by hypoxia/ischemia and improved their motor and cognitive behaviour [124]. In a currently ongoing Phase I clinical trial, Mancías-Guerra *et al.* [125] are assessing the safety, tolerability and efficiency of bone marrow-derived total nucleated cells, in patients diagnosed with cerebral palsy. Their preliminary results are

promising, with good safety results and improvement in neurological function.

CONCLUSION

Cerebral white matter injury following a hypoxic or ischemic insult during the neonatal period can lead to severe disability later on in life, both in terms of motor disorders and cognitive impairment. The nature of this condition is such that it does not only affect the patients. Its ramifications cause considerable burden upon the people closest to them and to society in general. Better understanding of the pathophysiology of this condition might give new insights in developing new therapeutic modalities for such a challenging disease. Moreover, identifying crucial prognostic factors that determine long-term neurodevelopment outcomes may possibly help identify individuals at risk. Such patients would benefit from proper rehabilitative care and better assistance throughout the early stages of development, thereby ameliorating their quality of life.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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